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Reserpine differentially affects cocaine-induced behavior in low and high responders to novelty

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ABSTRACT

Individuals are known to differ in their sensitivity to cocaine. Cocaine is known to inhibit the re-uptake of monoamines. The response to cocaine has also been found to depend on monoamines inside reserpine-sensitive storage vesicles. The present study examined the effects of reserpine (1–2 mg/kg) on cocaine-induced behavior (10–15 mg/kg) in Low Responders (LR) and High Responders (HR) to novelty rats. LR displayed less cocaine-induced walking, wall rearing, free rearing and stereotyped behavior than HR did. The dose of 1 mg/kg of reserpine decreased cocaine-induced walking, wall rearing, free rearing and stereotyped behavior in LR, but not in HR. A dose of 2 mg/kg of reserpine was required to inhibit cocaine-induced behavior in HR. Combining these behavioral findings with our previously reported neurochemical finding that a higher dose of reserpine was required to inhibit the accumbal dopamine response to cocaine in HR than in LR (Verheij et al., 2008), suggests that HR are more sensitive to the behavioral effects of cocaine than LR because cocaine can release more monoamines from storage vesicles in HR than in LR. Our behavioral data also demonstrate that the individual differences in sensitivity to reserpine are not only limited to the dopaminergic system of the nucleus accumbens.

1. Introduction

Individual differences in the susceptibility to psychostimulants have extensively been reported, both in humans (Ball et al., 1994; Gynther et al., 1995; Jaffe and Archer, 1987; van den Bree et al., 1998) and in animals (Mantsch et al., 2001; Piazza et al., 1989, 2000). In this study we focused on two types of rat that are known to differ in their acute response to cocaine (COC). These individuals, which co-exist in a normal outbred population of Wistar rats, are selected on the basis of their exploratory response in a novel environment and, accordingly, labeled low responders (LR) and high responders (HR) to novelty (Bevins et al., 1997; Cools et al., 1990; Cools and Gingras, 1998; Cools and Tuinstra, 2003; Dellu et al., 1996; Kabbaj, 2004; Piazza et al., 1989, 1991; Rouge-Pont et al., 1993; Verheij and Cools, 2008). These rats are generally referred to as an animal model for low and high sensation seeking in man (Ballaz et al., 2007a, 2007b; Cools and Ellenbroek, 2002; Dellu et al., 1996).

Previous studies have demonstrated that COC increases monoamine levels in the nucleus accumbens to a smaller degree in LR than in HR (Chefer et al., 2003; Hooks et al., 1991b; Verheij et al., 2008). In addition, the behavioral response to COC has been shown to be smaller in LR than in HR (Hooks et al., 1992, 1991a, 1991b). COC is known to inhibit the re-uptake of monoamines by blocking plasmalemmal monoamine transporters (Lee et al., 2001). However, both neurochemical and behavioral studies have demonstrated that the response to COC depends also on monoamines inside storage vesicles (Davis, 1985; Florin et al., 1995; Hurd and Ungerstedt, 1989; McMillen, 1983; McMillen et al., 1980; Pifl et al., 1995; Scheel-Kruger et al., 1977; Venton et al., 2006; Verheij et al., 2008). We have recently demonstrated that the monoaminergic storage pools of the nucleus accumbens of LR are smaller than the monoaminergic storage pools of the nucleus accumbens of HR (Cools and Verheij, 2002; Verheij and Cools, 2009b; Verheij et al., 2008). We have, therefore, proposed that LR are less sensitive to the neurochemical effects of COC than HR, because COC can release less monoamines from storage vesicles in LR than in HR (Verheij and Cools, 2008; Verheij et al., 2008).

In the present study we have used the indole alkaloid reserpine (RES). RES binds to vesicular monoamine transporters (Henry et al., 1998; Kirshner et al., 1963). After RES treatment, monoaminergic storage vesicles are known to become empty (Colliver et al., 2000; Dahlstrom et al., 1965; Gong et al., 2003; Pothos et al., 1998; Wagner, 1985). Following the dose of 1 mg/kg of RES, COC could still increase the levels of accumbal dopamine in HR, but not in LR rats (Verheij

Abbreviations: COC, cocaine; HR, High Responders to novelty; LR, Low Responders to novelty; RES, reserpine.

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et al., 2008). A higher dose of 2 mg/kg of RES was needed to inhibit the COC-induced increase of accumbal dopamine in HR (Verheij et al., 2008). The aim of the present study was to analyze whether these individual differences in the sensitivity to RES do exist not only at the neurochemical level, but also at the behavioral level. The expected RES-induced changes in behavior demonstrate that the RES-induced neurochemical changes are functional. Based on our neurochemical findings, we hypothesized that COC-treated LR are more sensitive to the behavioral effects of RES than COC-treated HR.

2. Methods

2.1. Subjects

Adult male LR ($n=41$) and HR ($n=64$) that were selected from the outbred strain of Nijmegen Wistar rats were used throughout the study. Apart from the assessment of the behavioral response to COC, these rats were also used to measure the COC-induced changes of accumbal dopamine (see Introduction). The results of this neurochemical analysis have been published in a separate paper (Verheij et al., 2008). All rats (weight = 180–220 g) were reared and housed in macrolon cages (42×26×15 cm; $n=3$–4 per cage) under a fixed 12/12 h light/dark cycle (lights on: 07.00 a.m.) in a temperature-controlled room (21±1.7 °C). Water and food pellets were available *ad libitum*. The experiments were performed in accordance with institutional, national and international guidelines for animal care and welfare. All procedures were in agreement with the NRC (National Research Council) 2003 guidelines for the care and use of mammals in neuroscience and behavioral research and the European communities council directive of 24 November 1986 (86/609/EEC). Every effort was made to minimize the number of animals used and their suffering.

2.2. Open-field selection

Rats were individually housed 3 days before the open-field selection procedure (Verheij et al., 2008). Testing took place between 09.00 h and 17.00 h in a room illuminated by white light of 170 lx. The rat was placed on a black, square table (160×160 cm) made of Perspex. This open-field is 95 cm elevated above the floor and surrounded by a white neutral background (270×270×270 cm). Behavior was recorded with a computerized automated tracking system for a period of 30 min. The objective parameters of ambulation and habituation time were used to select LR and HR (see also: Cools et al., 1990; Ellenbroek and Cools, 2002). Ambulation was defined as the overall distance (cm) traveled in 30 min. Habituation time was defined as the duration of the period (s) that started as soon as the rat began to explore the open-field and ended as soon as the locomotor activity stopped for at least 90 s. Rats that habituated in less than 480 s and walked less than 4800 cm in 30 min were labeled LR, whereas rats that habituated after 840 s and walked more than 6000 cm in 30 min were labeled HR (see also: Verheij et al., 2008). Habituation time in addition to ambulation was used as selection criterion, because traveled distance per se is not always a reliable criterion (Cools et al., 1997; Saigusa et al., 1999). To select extremes in ambulation we used fixed criteria, instead of a split that is based on mean ambulation, because the mean of ambulation may well differ between rats of different breeders (Ellenbroek and Cools, 2002). Typically, 40–50% of the rats within a Wistar population do not fit our criteria (see Results) and are excluded from analysis. Efforts were made to include these animals in other studies (Verheij et al., 2007).

2.3. Reserpine and cocaine treatment

At 12.00 h on the first day of the experiment, LR and HR were injected with RES or its solvent. After this systemic injection (volume: 1 ml/kg, i.p.), rats were returned to their home cage and left undisturbed. At 12.00 h on the second day of the experiment, a systemic injection (volume 1 ml/kg, i.p.) of COC or its solvent (saline) was given. Rats were exposed to a new cage immediately after their second injection. This novel cage was slightly larger than the home cage (new dimensions: 30×30×35 cm) and lacked sawdust on the floor.

2.4. Doses of reserpine

Both LR and HR were injected with 1 mg/kg of RES (Daiichi, Tokyo, Japan) on day 1 and 10 or 15 mg/kg of COC (Brocacef, Amsterdam, The Netherlands) on day 2. Because the dose of 1 mg/kg of RES was found to have no effect on the COC-induced neurochemical changes in HR (Verheij et al., 2008), an additional group of HR was pretreated with a

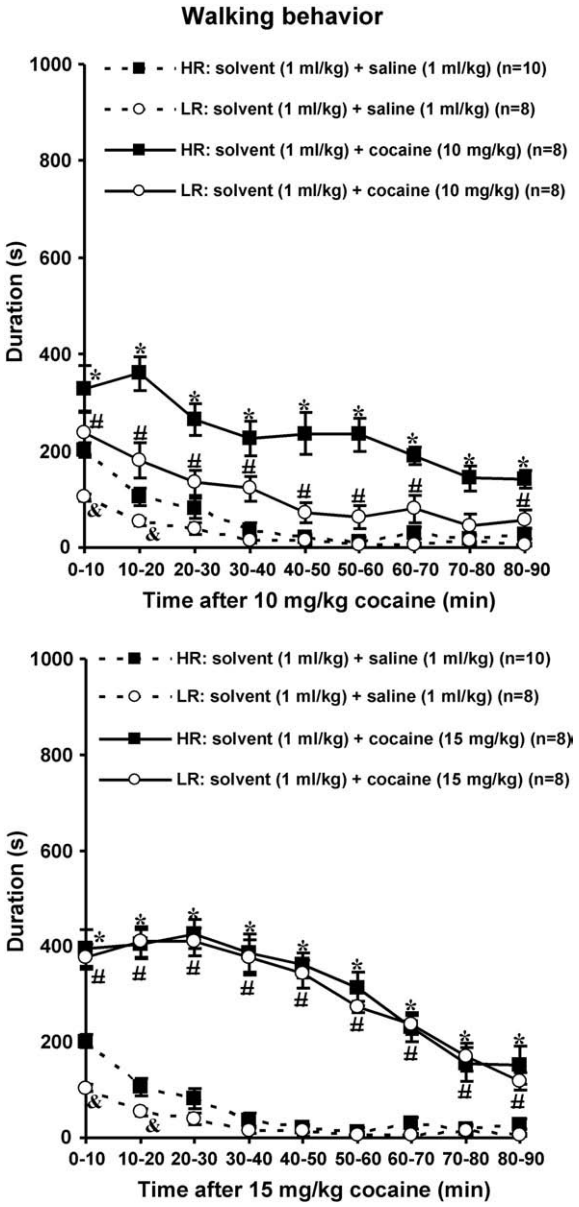

Fig. 1. Effects of saline (upper/lower panel), 10 mg/kg (upper panel) and 15 mg/kg (lower panel) of cocaine on the duration (s) of walking behavior in LR (circle) and HR (square). Cocaine-treated rats are represented by a filled line, saline-treated rats are represented by a dotted line. All rats were pretreated with the solvent of reserpine (=solvent) 24 h before saline or cocaine was given. Data are expressed as mean±SEM. LR = Low Responders to novelty, HR = High Responders to novelty. # = Significant difference between cocaine-treated and saline-treated LR (Student's *t*-test), * = Significant difference between cocaine-treated and saline-treated HR (Student's *t*-test), & = Significant difference between saline-treated LR and saline-treated HR (Student's *t*-test).

dose of 2 mg/kg of RES on day 1.The relatively low doses of 1 and 2 mg/kg of RES were chosen because it has previously been demonstrated that these doses were effective in depleting RES-sensitive monoaminergic storage vesicles (Verheij and Cools, 2007; Verheij and Cools, 2009a, 2009b; Verheij et al., 2008).

2.5. Behavior

Behavior was recorded on video tape and analyzed offline by an observer blind to the type of rat and its treatment, using a computer program (KEYS®) developed at our institute (Saigusa et al., 1999). Recordings were made directly after the administration of COC for a period of 90 min. Given that the studies by Hooks et al., revealing individual differences in the behavioral response to COC (see Introduction), were studies using a general measure of activity (photocell counts), the present study measured activity in more detail. The duration of the following behavioral items was scored: walking (displacement of all 4 paws over a minimum distance of 1 cm for a period of at least 3 s), wall rearing (front paw(s) raised against the side wall(s) of the cage), free rearing (front paw(s) raised off the cage floor without touching a side wall of the cage) and grooming (washing any part of the body). In addition, the frequency of wall rearing and free rearing was calculated. These behavioral items were chosen because the COC-induced changes on these behaviors may very well be mediated by different neuronal substrates (see Discussion).

2.6. Statistical analysis and expression of the data

Behavior was expressed as the mean duration ± SEM per block of 10 min. The behavioral effects were statistically compared, using a three-way ANOVA with the factors type of rat (levels: HR and LR), treatment (levels: 0, 10 and 15 mg/kg of COC) and time for repeated measures (levels: 0–10, 10–20, 20–30, 30–40, 40–50, 50–60, 60–70, 70–80 and 80–90 min). This ANOVA was followed by a two-way ANOVA (factors: treatment and time for repeated measures) and a post-hoc Student's *t*-test where appropriate. SPSS for Windows (Release 12.0) was used to statistically analyze the data. A probability level of $p<0.05$ was taken as significant in every test.

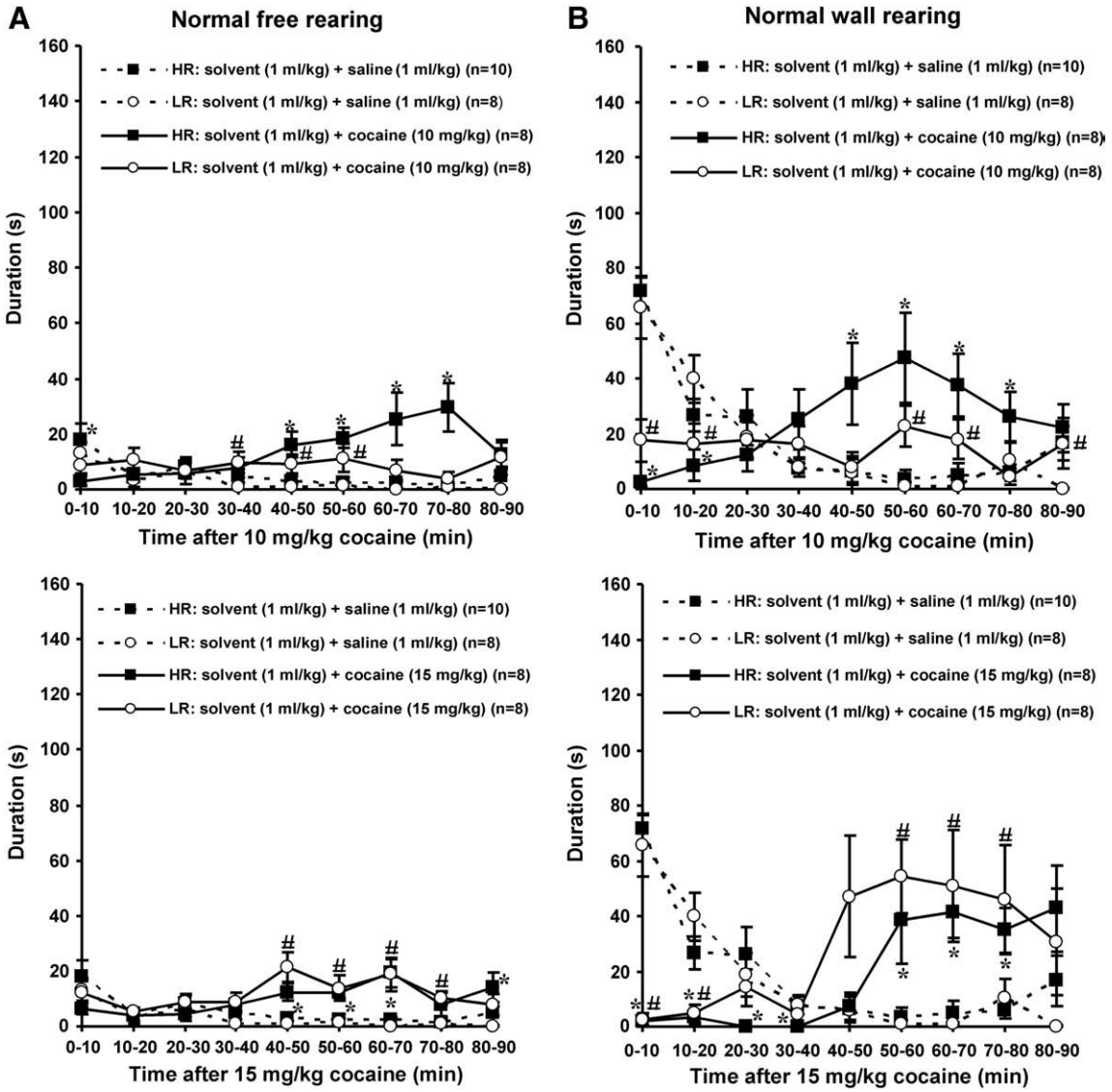

Fig. 2. Effects of saline (upper/lower panel), 10 mg/kg (upper panel) and 15 mg/kg (lower panel) of cocaine on the duration (s) of normal free rearing (Fig. 2A) and normal wall rearing (Fig. 2B) in LR (circle) and HR (square). Cocaine-treated rats are represented by a filled line, saline-treated rats are represented by a dotted line. All rats were pretreated with the solvent of reserpine (= solvent) 24 h before saline or cocaine was given. Data are expressed as mean ± SEM. LR = Low Responders to novelty, HR = High Responders to novelty. # = Significant difference between cocaine-treated and saline-treated LR (Student's *t*-test), * = Significant difference between cocaine-treated and saline-treated HR (Student's *t*-test).

3. Results

3.1. Open-field selection

The open-field selection procedure provided 22% LR ($n=41$) and 35% HR ($n=64$). The average distance traveled in 30 min (±SEM) was 3757±152 cm and 8260±269 cm in LR and HR respectively. The average habituation time (±SEM) was 392±20 s in LR and 1323±52 s in HR. Rats that did not fulfill the criteria (43% of the population) were not included in this study.

3.2. Two types of rearing

The duration of every single rearing bout was analyzed. The mean duration of a single rearing bout after saline was 5.0±0.2 s. In case the duration of a single rearing bout after COC was not different from the mean duration of the single rearing bouts after saline (z-score<1.96, $p>0.05$), this rearing bout was labeled 'normal'. Both the dose of 10 and the dose of 15 mg/kg of COC resulted in normal rearing. Rats treated with 15 mg/kg of COC also displayed another type of rearing. The duration of a single rearing bout of this type was significantly less than the mean duration of the single rearing bouts after saline (z-score>1.96, $p<0.05$). Because of the high frequency of this type of rearing (to be discussed in the later part), these rearing bouts were labeled 'repetitive'.

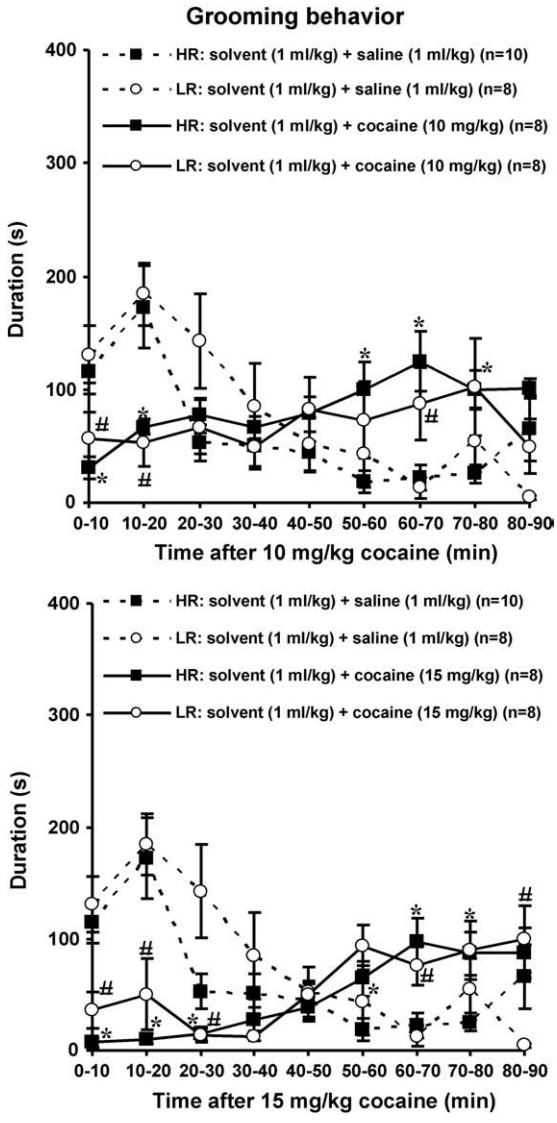

Fig. 3. Effects of saline (upper/lower panel), 10 mg/kg (upper panel) and 15 mg/kg (lower panel) of cocaine on the duration (s) of grooming behavior in LR (circle) and HR (square). Cocaine-treated rats are represented by a filled line, saline-treated rats are represented by a dotted line. All rats were pretreated with the solvent of reserpine (= solvent) 24 h before saline or cocaine was given. Data are expressed as mean±SEM. LR = Low Responders to novelty, HR = High Responders to novelty. # = Significant difference between cocaine-treated and saline-treated LR (Student's t-test), * = Significant difference between cocaine-treated and saline-treated HR (Student's t-test).

3.3. Description of normal and repetitive rearing

To verify that normal rearing was different from repetitive rearing, the frequency and total duration of both types of behavior were analyzed. Given that only rats that were treated with 15 mg/kg of COC displayed repetitive rearing (as previously discussed), this analysis of rearing was restricted to this single dose of COC. The maximum frequency of normal rearing following 15 mg/kg of COC was 16±3 rearing acts per 10 min and the average duration of a single rearing bout of this type was 4.6±0.4 s. Rats spent a total time of 213±34 s on normal rearing. The maximum frequency of repetitive rearing following 15 mg/kg of COC was 94±12 rearing acts per 10 min (this was significantly higher than the maximum frequency of normal rearing: Student's t-test: $p<0.05$) and the average duration of a single rearing bout of this type was only 1.3±0.1 s (this was significantly less than the average duration of a single bout of normal rearing: Student's t-test: $p<0.05$). Rats spent a total time of 388±68 s on repetitive rearing (this was significantly more than the total time of normal rearing: Student's t-test: $p<0.05$). Normal rearing consisted of both free and wall rearing whereas repetitive rearing was directed only to the wall.

3.4. Behavioral changes after cocaine

The behavioral effects of COC are depicted in Figs. 1–4 (Fig. 1: walking, Fig. 2A: normal free rearing, Fig. 2B: normal wall rearing, Fig. 3: grooming and Fig. 4: repetitive wall rearing). It has previously been shown that the behavioral effects of low and high doses of COC are mediated by distinct neuronal substrates (Carboni et al., 1989; Di Chiara and Imperato, 1988). For this reason, the effects of COC were analyzed per single dose (to be discussed in the later part). A summary of this statistical analysis (three-way ANOVA for repeated measures) is provided in Table 2 (rat type×treatment (× time) effects) and Table 1 (treatment (× time) effects). Because LR and HR have previously been found to differ in their sensitivity to COC (Hooks et al., 1992, 1991a, 1991b), the RES-induced changes in COC-induced behavior were analyzed per type of rat (to be discussed in the later part). A summary of this statistical analysis (two-way ANOVA for repeated measures) is provided in Table 3 (treatment (× time) effects).

3.4.1. Treatment effects of saline

Figs. 1–4 illustrate that the duration of all behavioral items, apart from repetitive wall rearing, was increased in rats that were treated with saline (Table 1).

3.4.2. Treatment effects of cocaine

Figs. 1 and 2A show that both the dose of 10 mg/kg of COC and the dose of 15 mg/kg of COC increased walking and normal free rearing (Table 1). Both doses of COC changed normal wall rearing and grooming in a time-dependent manner (Table 1). Figs. 2B and 3 show that the effects of COC on normal wall rearing and grooming were biphasic. COC decreased normal wall rearing between 0 and 30 min (Table 1) and grooming between 0 and 40 min (Table 1) and increased normal wall rearing between 30 and 90 min (Table 1) and grooming between 40 and 90 min (Table 1). The transition points (30 min for normal wall rearing and 40 min for grooming) were arbitrarily chosen on the basis of the time course that was found (see Figs. 2B and 3). Fig. 4 illustrates that rats treated with 10 mg/kg of COC did not display repetitive wall rearing (Table 1) whereas this type of rearing did increase in rats treated with 15 mg/kg of COC (Table 1).

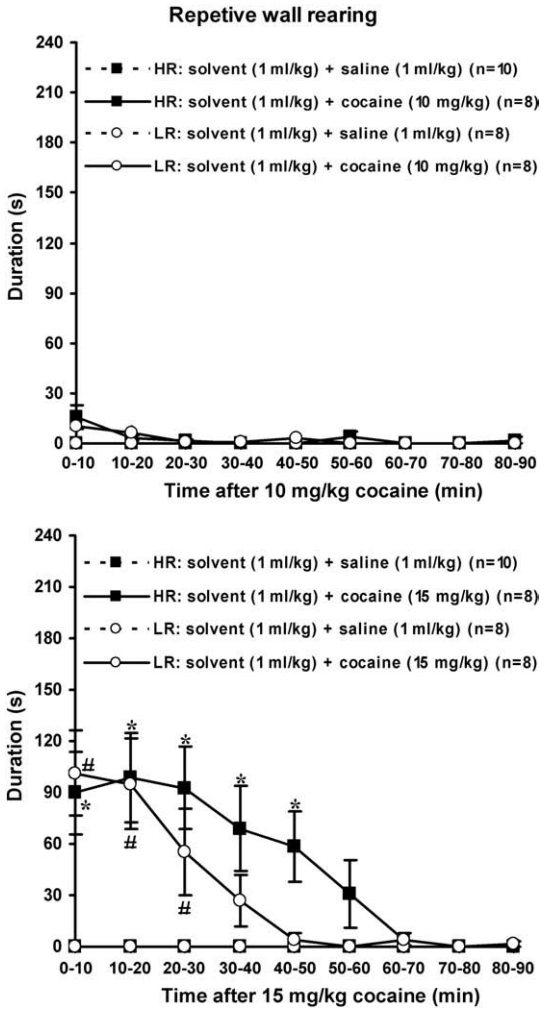

Fig. 4. Effects of saline (upper/lower panel), 10 mg/kg (upper panel) and 15 mg/kg (lower panel) of cocaine on the duration (s) of repetitive wall rearing in LR (circle) and HR (square). Rats treated with saline or 10 mg/kg of cocaine did not show repetitive wall rearing. All rats were pretreated with the solvent of reserpine (= solvent) 24 h before cocaine was given. Data are expressed as mean ± SEM. LR = Low Responders to novelty, HR = High Responders to novelty. # = Significant difference between cocaine-treated and saline-treated LR (Student's *t*-test), * = Significant difference between cocaine-treated and saline-treated HR (Student's *t*-test).

3.4.3. Rat type effects of saline

In the rats that were treated with saline (the solvent of COC), rat type effects were found only for walking behavior. Fig. 1 illustrates that walking increased less in saline-treated LR than in saline-treated HR (Table 2). These individual differences in walking behavior were limited to the first 20 min (Student's *t*-test). No differences were found between saline-treated LR and saline-treaded HR for the remaining behavioral items (Table 2).

3.4.4. Rat type effects of 10 mg/kg of cocaine

In rats that were treated with the relatively moderate dose of 10 mg/kg of COC, rat type effects were found for walking, normal free rearing and normal wall rearing. Figs. 1 and 2A demonstrate that walking and normal free rearing increased less in LR than in HR (Table 2). It is important to note that COC still resulted in individual differences in walking behavior, even during the period that saline-treated LR did not anymore differ from saline-treated HR (see Fig. 1, time ≥ 30 min). Analysis of the first period of normal wall rearing (see Fig. 2B) revealed that the decrease of this behavior did not differ between the two types of rat (Table 2) whereas the increase of normal wall rearing in the second period was less in LR compared to HR (Table 2). Analysis of the first and second period of grooming (see Fig. 3) revealed that both the decrease and the increase of this behavior did not differ between the two types of rat (Table 2). Given that rats that were treated with 10 mg/kg of COC did not display repetitive wall rearing (as previously discussed), no rat type effects were found for this behavioral item (Table 2).

3.4.5. Rat type effects of 15 mg/kg of cocaine

In the rats that were treated with the relatively high dose of 15 mg/kg of COC, rat type effects were found for repetitive wall rearing. Fig. 4 illustrates that this dose of COC increased repetitive wall rearing less in LR than in HR (Table 2). Figs. 1–3 illustrate that 15 mg/kg of COC did not result in rat type effects for the remaining behavioral items (Table 2).

3.5. Behavioral changes after reserpine

Figs. 5–8 show the effects of 1 mg/kg of RES on COC-induced behavior (Fig. 5A/B: walking, Fig. 6A/B: normal free and normal wall rearing, Fig. 7A/B: grooming and Fig. 8: repetitive wall rearing). A summary of the statistical analysis is provided in Table 3.

3.5.1. Effects of 1 mg/kg of reserpine on cocaine-induced behavior

3.5.1.1. Effects of 1 mg/kg of reserpine in LR. The relatively low dose of 1 mg/kg of RES changed all behavioral items in COC-treated LR.

Table 1
Treatment effects per single dose of cocaine. The dose of 0 mg/kg of cocaine was statistically compared with either the dose of 10 mg/kg of cocaine or the dose of 15 mg/kg of cocaine (ANOVA for repeated measures). For both doses of cocaine, treatment × time effects (df = 8) were found for walking, normal free rearing, normal wall rearing and grooming. Treatment × time effects (df = 8) were also found for repetitive wall rearing after 15 mg/kg of cocaine, but not after 10 mg/kg of this drug. For saline, time effects (df = 8) were found for all behavioral items, except for repetitive wall rearing. The treatment effects of both doses of cocaine on normal wall rearing were biphasic. Normal wall rearing decreased between 0 and 30 min (df = 2) and increased between 30 and 90 min (df = 6). The treatment effects of both doses of cocaine on grooming were also biphasic. Grooming decreased between 0 and 40 min (df = 3) and increased between 40 and 90 min (df = 5). ↑ = significant saline or cocaine-induced increase of behavior, ↓ = significant cocaine-induced decrease of behavior, ↓↑ = significant cocaine-induced decrease followed by a significant cocaine-induced increase of behavior, x = non significant (n.s.) change of behavior.

Dose of cocaine	Walking: Fig.1	Normal free rearing: Fig. 2A	Normal wall rearing: Fig. 2B	Grooming: Fig. 3	Repetitive wall rearing: Fig. 4
0 mg/kg (saline)	0–90min: ↑ $F_{(8,128)} = 46.253$, $p<0.001$	0–90min: ↑ $F_{(8,128)} = 6.766$, $p<0.001$	0–90min: $F_{(8,128)} = 34.257$, $p<0.001$ ↑	0–90min: $F_{(8,128)} = 9.111$, $p<0.001$ ↑	n.s. x
10 mg/kg	0–90min: ↑ $F_{(8,240)} = 3.731$, $p<0.001$	0–90min: ↑ $F_{(8,240)} = 6.430$, $p<0.001$	0–90min: $F_{(8,240)} = 21.056$, $p<0.001$ ↓↑ 0–30min: $F_{(2,60)} = 21.266$, $p<0.001$ ↓ 30–90min: $F_{(6,180)} = 5.271$, $p<0.001$ ↑	0–90min: $F_{(8,240)} = 8.976$, $p<0.001$ ↓↑ 0–40min: $F_{(3,90)} = 4.989$, $p=0.003$ ↓ 40–90min: $F_{(5,150)} = 2.395$, $p=0.040$ ↑	n.s. x
15 mg/kg	0–90min: ↑ $F_{(8,240)} = 24.006$, $p<0.001$	0–90min: ↑ $F_{(8,240)} = 5.067$, $p<0.001$	0–90min: $F_{(8,240)} = 19.162$, $p<0.001$ ↓↑ 0–30min: $F_{(2,60)} = 29.480$, $p<0.001$ ↓ 30–90min: $F_{(6,180)} = 6.943$, $p<0.001$ ↑	0–90min: $F_{(8,240)} = 13.920$, $p<0.001$ ↓↑ 0–40mm: $F_{(3,90)} = 3.625$, $p=0.016$ ↓ 40–90min: $F_{(5,150)} = 5.300$, $p<0.001$ ↑	0–90min: ↑ $F_{(8,240)} = 15.847$, $p<0.001$

Table 2
Rat type effects per single doses of cocaine: The effects of cocaine were compared between LR and HR (ANOVA for repeated measures). Cocaine resulted in rat type × treatment × time effects (df > 1) or rat type × treatment effects (df = 1) for walking, normal free rearing, normal wall rearing and repetitive wall rearing. Rat type × time effects (df = 8) were found for walking in saline-treated rats. LR < HR: significant smaller effects of saline or cocaine in LR than in HR, LR = HR: similar effects of saline or cocaine in LR and HR (= non significant (n.s.) rat type × treatment × (time) effect).

Dose of cocaine	Walking Fig. 1		Normal free rearing: Fig. 2A		Normal wall rearing: Fig. 2B		Grooming: Fig. 3		Repetitive wall rearing: Fig. 4	
0 mg/kg (saline)	0–90min: $F_{(8,128)} = 4.766$, $p < 0.001$	LR<HR	n.s.	LR = HR	n.s.	LR = HR	n.s.	LR = HR	n.s.	LR = HR
10 mg/kg	0–90min: $F_{(8,240)} = 2.115$, $p = 0.035$	LR<HR	0–90min: $F_{(8,240)} = 3.260$, $p = 0.002$	LR<HR	0–30 min: n.s. 30–90 min: $F_{(6,180)} = 2.357$, $p = 0.032$	LR = HR LR<HR	n.s.	LR = HR	n.s.	LR = HR
15 mg/kg	n.s.	LR<HR	n.s.	LR = HR	0–40 min: n.s. 40–90 min: n.s.	LR = HR LR = HR	n.s.	LR = HR	0–90min: $F_{(1,14)} = 5.408$, $p = 0.036$	LR<HR

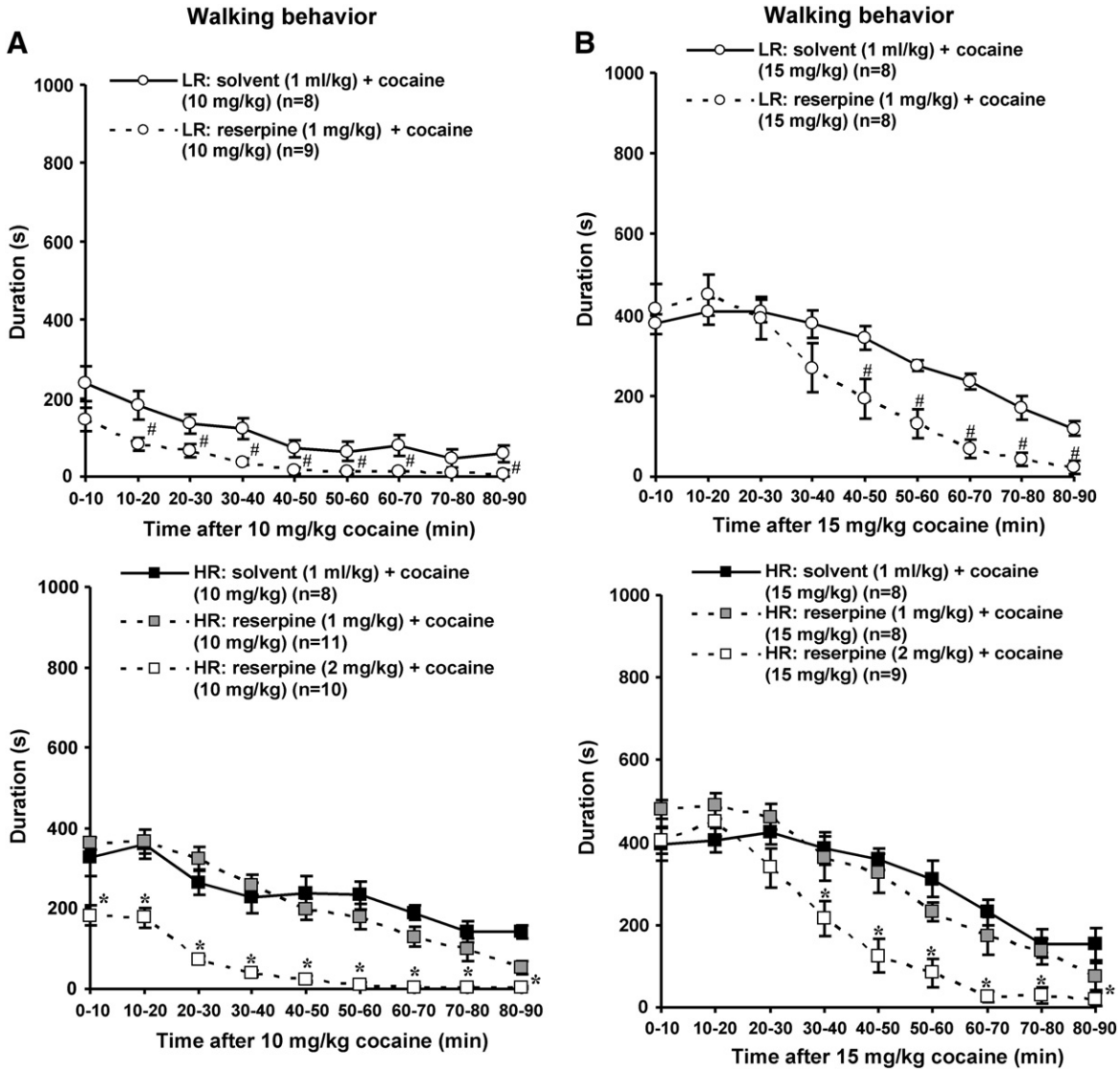

Fig. 5. Effects of reserpine on the duration (s) of walking elicited by 10 mg/kg (Fig. 5A) and 15 mg/kg (Fig. 5B) of cocaine in LR (upper panel) and HR (lower panel). Rats treated with reserpine-solvent and cocaine are represented by a filled line, rats treated with reserpine and cocaine are represented by a dotted line. The effective dose of reserpine (1 mg/kg in LR and 2 mg/kg in HR) is displayed in white symbols whereas the non-effective dose of reserpine (1 mg/kg in HR) is displayed in grey symbols. Data are expressed as mean ± SEM. LR = Low Responders to novelty, HR = High Responders to novelty. # = Significant effect of reserpine in cocaine-treated LR (Student's *t*-test), * = Significant effect of reserpine in cocaine-treated HR (Student's *t*-test).

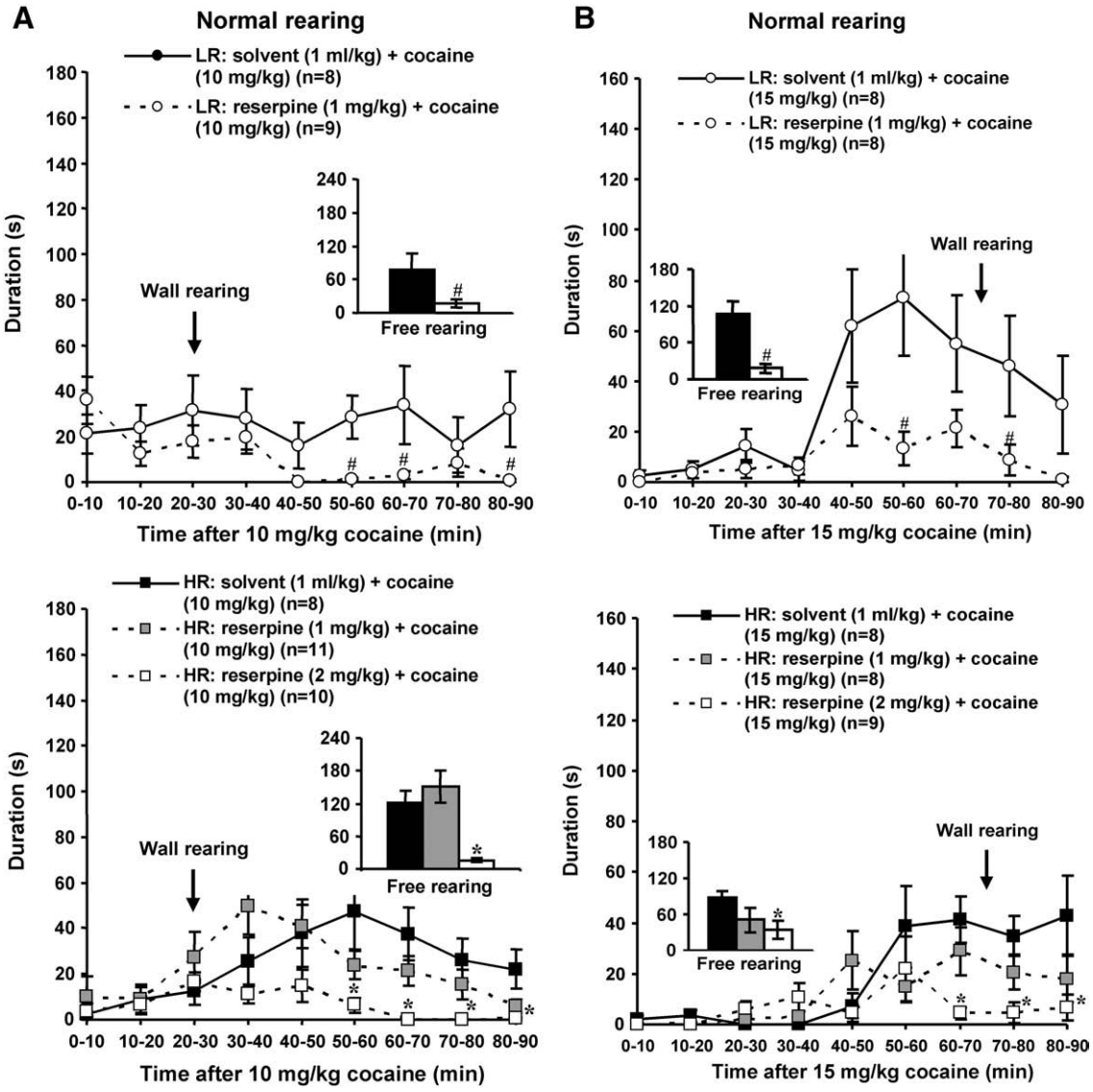

Fig. 6. Effects of reserpine on the duration (s) of normal free rearing (inlay) and normal wall rearing (main graph) elicited by 10 mg/kg (Fig. 6A) and 15 mg/kg (Fig. 6B) of cocaine in LR (upper panel) and HR (lower panel). Rats treated with reserpine-solvent and cocaine are represented by a filled line, rats treated with reserpine and cocaine are represented by a dotted line. The effective dose of reserpine (1 mg/kg in LR and 2 mg/kg in HR) is displayed in white symbols whereas the non-effective dose of reserpine (1 mg/kg in HR) is displayed in grey symbols. Data are expressed as mean ± SEM. LR = Low Responders to novelty, HR = High Responders to novelty. # = Significant effect of reserpine in cocaine-treated LR (Student's *t*-test), * = Significant effect of reserpine in cocaine-treated HR (Student's *t*-test).

Figs. 5–8 illustrate that this low dose of RES reduced walking (Table 3), normal free rearing (Table 3), normal wall rearing (Table 3) and repetitive wall rearing (Table 3) in these rats, but increased grooming (Table 3).

3.5.1.2. Effects of 1 mg/kg of reserpine in HR. Figs. 5–8 revealed that none of the behavioral items were affected by the relatively low dose of 1 mg/kg of RES in COC-treated HR (Table 3).

3.5.2. Effects of 2 mg/kg of reserpine on cocaine-induced behavior in HR

To rule out that COC-induced behavior in HR is not at all dependent on RES-sensitive storage vesicles, a new group of these rats was pretreated with a higher dose of RES. The effects of 2 mg/kg of RES on COC-induced behavior in HR are also depicted in Figs. 5–8 (Fig. 5A/B: walking, Fig. 6A/B: normal free and normal wall rearing, Fig. 7A/B: grooming and Fig. 8: repetitive wall rearing). A summary of the statistical analysis is provided in Table 3.

The relatively high dose of 2 mg/kg of RES changed 4 out of the 5 behavioral items in COC-treated HR. Figs. 5–7 illustrate that the high dose of RES reduced walking (Table 3), normal free rearing (Table 3) and normal wall rearing (Table 3) in these rats, but increased grooming (Table 3). Fig. 8 shows that the relatively high dose of RES did not change repetitive wall rearing (Table 3).

4. Discussion

4.1. Treatment effects of cocaine (see Table 1 for summary)

COC increased walking (Fig. 1), normal free rearing (Fig. 2A) and repetitive wall rearing (Fig. 4). The effects of COC on normal wall rearing (Fig. 2B) and grooming (Fig. 3) appeared to be biphasic. These two behavioral items initially decreased and subsequently increased. Given that especially walking and repetitive wall rearing dominated behavior immediately after the administration of COC, the execution of these behavioral items might initially have prevented normal wall rearing and grooming to take place (behavioral competition). According to this reasoning, normal wall rearing and grooming could only appear once walking and repetitive wall rearing started to decrease.

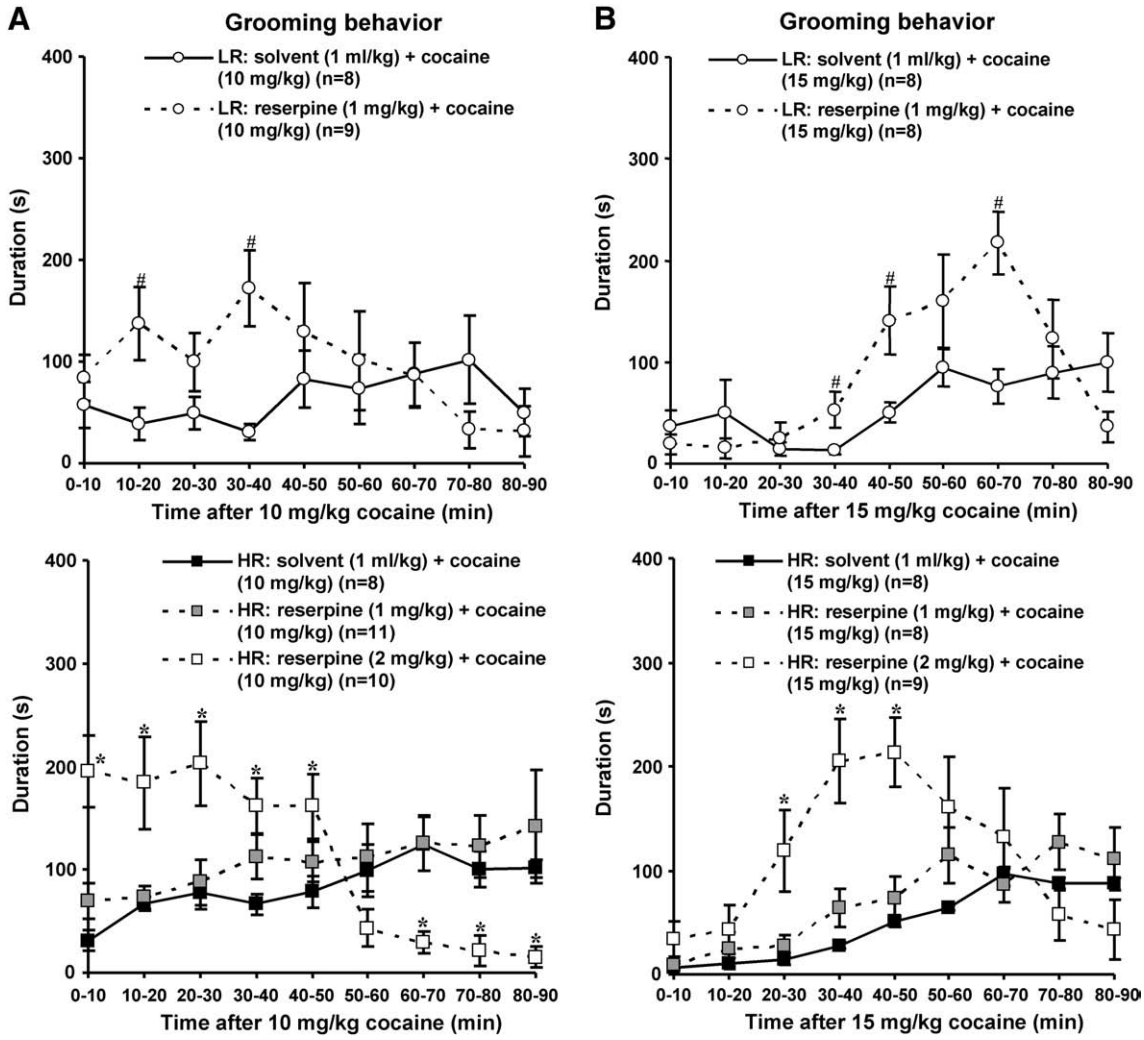

Fig. 7. Effects of reserpine on the duration (s) of grooming behavior elicited by 10 mg/kg (Fig. 7A) and 15 mg/kg (Fig. 7B) of cocaine in LR (upper panel) and HR (lower panel). Rats treated with reserpine-solvent and cocaine are represented by a filled line, rats treated with reserpine and cocaine are represented by a dotted line. The effective dose of reserpine (1 mg/kg in LR and 2 mg/kg in HR) is displayed in white symbols whereas the non-effective dose of reserpine (1 mg/kg in HR) is displayed in grey symbols. Data are expressed as mean ± SEM. LR = Low Responders to novelty, HR = High Responders to novelty. # = Significant effect of reserpine in cocaine-treated LR (Student's *t*-test), * = Significant effect of reserpine in cocaine-treated HR (Student's *t*-test).

In contrast to normal free/wall rearing that was marked by a low frequency and a short total duration, repetitive wall rearing was marked by a high frequency and a long total duration (see Results). Because stereotyped behavior has been defined as behavior that is continuously repeated and lasts for a long period of time (Ellenbroek and Cools, 1993), the observed COC-induced changes in repetitive wall rearing are supposed to reflect stereotypic behavior. Given that rats exposed to a new environment express high levels of normal rearing and walking (Saigusa et al., 1999), the observed COC-induced changes in these behavioral items may very well reflect normal exploration behavior. The finding that COC strongly increased stereotypic wall rearing and walking whereas normal rearing and grooming were simultaneously reduced supports the early work of Lyon and Robbins (1975) showing that increasing doses of psychostimulants cause an organism to exhibit increasing behavioral response rates within a decreasing number of response categories.

4.2. Rat type effects of cocaine (see Table 2 for summary)

LR treated with the solvent of COC displayed less walking than HR treated with the solvent of COC (Fig. 1), whereas the duration of the remaining behavioral items did not differ between saline-treated LR and HR (Figs. 2–4). The moderate dose of 10 mg/kg of COC increased walking (Fig. 1), normal free rearing (Fig. 2A) and normal wall rearing (Fig. 2B) to a smaller degree in LR than in HR. Similar to saline, the dose of 15 mg/kg of COC resulted in individual differences in one behavioral item only. This higher dose of COC increased repetitive wall rearing less in LR than in HR (Fig. 4). Our results fit in with the previously reported finding that COC increases general activity (photocell counts) less strongly in LR than in HR (Hooks et al., 1992, 1991a, 1991b). The present findings also confirm our previously reported notion (Cools et al., 1997) that the behavioral differences between LR and HR are particularly evident in case these rats are exposed to intermediate (pharmacological) challenges (injection of 10 mg/kg of COC) and become less when the challenge is either too small (saline injection) or too large (injection of 15 mg/kg of COC).

4.3. Effects of reserpine on cocaine-induced walking and rearing (see Table 3 for summary)

The dose of 1 mg/kg of RES reduced COC-induced walking, normal free rearing and normal wall rearing in LR (Figs. 5–6), but had no effect on these behaviors in HR (Figs. 5–6). Only the higher dose of 2 mg/kg of RES was able to reduce COC-induced walking, normal free rearing and normal wall rearing in HR (Figs. 5–6). Neither 1 nor 2 mg/

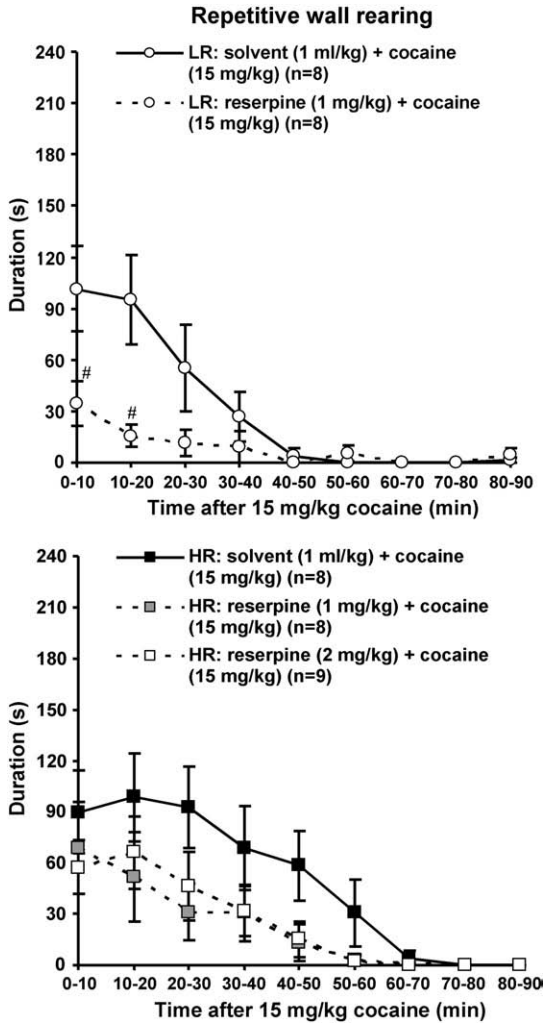

Fig. 8. Effects of reserpine on the duration (s) of repetitive wall rearing elicited by 15 mg/kg of cocaine in LR (upper panel) and HR (lower panel). Rats treated with reserpine-solvent and cocaine are represented by a filled line, rats treated with reserpine and cocaine are represented by a dotted line. The dose of 10 mg/kg of cocaine did not induce repetitive wall rearing (see Fig. 4). Data are expressed as mean ± SEM. LR = Low Responders to novelty, HR = High Responders to novelty. # = Significant effect of reserpine in cocaine-treated LR (Student's *t*-test), No significant effect of reserpine in cocaine-treated HR (Student's *t*-test).

kg of RES affected COC-induced repetitive wall rearing in HR, whereas 1 mg/kg of RES already decreased this behavior in LR (Fig. 8). These data provide evidence in favor of our hypothesis (see Introduction) that COC-treated LR are more sensitive to the behavioral effects of RES than COC-treated HR. The fact that RES, which depletes vesicular monoamines, decreased COC-induced walking and rearing suggests that these COC-induced behaviors are accompanied by an increased release of monoamines from storage vesicles.

The present data indicate that COC-induced walking and normal free/wall rearing are mediated by a substrate that is different from the substrate involved in COC-induced repetitive wall rearing. First, 10 mg/kg of COC did not increase the duration of repetitive wall rearing in LR or in HR (Fig. 4 and Table 1). In contrast, this dose of COC strongly increased the duration of walking and normal free/wall rearing in both types of rat (Figs. 1–2 and Table 1). Second, the dose of 15 mg/kg of COC resulted in individual differences in repetitive wall rearing (Fig. 4 and Table 2), but this dose of COC did not result in individual differences in walking and normal free/wall rearing (Figs. 1–2 and Table 2). Third, 2 mg/kg of RES did not alter COC-induced repetitive wall rearing in HR (Fig. 8 and Table 3). However, this dose of RES strongly reduced COC-induced walking and normal free/wall rearing in these rats (Figs. 5–6 and Table 3).

4.4. Effects of reserpine on cocaine-induced grooming (see Table 3 for summary)

The dose of 1 mg/kg of RES increased COC-induced grooming in LR, but had no effect on this behavior in HR (Fig. 7). Only the higher dose of 2 mg/kg of RES was able to increase COC-induced grooming in HR (Fig. 7). These data underline that COC-treated LR are more sensitive to the behavioral effects of RES than COC-treated HR. The fact that RES, which depletes vesicular monoamines, increases COC-induced grooming suggests that COC-induced grooming is accompanied by a decreased release of monoamines from storage vesicles. The notion that COC-induced walking, normal free/wall rearing and repetitive wall rearing are all accompanied by a monoamine increase (see Section 4.3), suggests that COC-induced grooming is mediated by a third substrate that differs from the substrates involved in either COC-induced walking and normal free/wall rearing or COC-induced repetitive wall rearing.

4.5. Methodological considerations

High doses of RES may inhibit motor behavior by increasing muscle rigidity (Jurna, 1976). This impaired motor performance is typically observed after the intraperitoneal administration of (more than) 10 mg/kg of RES (Johnels, 1983; Johnels et al., 1978; Southwick

Table 3
Treatment effects of reserpine per type of rat: The effects of reserpine + cocaine were compared to the effects of solvent + cocaine (ANOVA for repeated measures). For the dose of 1 mg/kg of reserpine, treatment × time effects (df = 8) or treatment effects (df = 1) were found for all behavioral items in LR, but for none of the behavioral items in HR. The dose of 2 mg/kg of reserpine resulted in treatment × time effects (df = 8) or treatment effects (df = 1) for all behavioral items, except for repetitive wall rearing, in HR. ↑ = significant reserpine-induced increase of behavior, ↓ = significant reserpine-induced decrease of behavior, x = non significant (n.s.) change of behavior.

Type of rat	Dose of reserpine	Dose of cocaine	Walking: Fig. 5	Normal free rearing: Fig. 6	Normal wall rearing: Fig. 6	Grooming: Fig. 7	Repetitive wall rearing: Fig. 8
LR	1 mg/kg	10 mg/kg	$F_{(1,15)} = 8.178$, $p = 0.012$ ↓	$F_{(1,15)} = 5.016$, $p = 0.041$ ↓	$F_{(8,120)} = 2.420$, $p = 0.019$ ↓	$F_{(8,120)} = 2.086$, $p = 0.042$ ↑	n.s. x
LR	1 mg/kg	15 mg/kg	$F_{(8,112)} = 4.352$, $p < 0.001$ ↓	$F_{(1,14)} = 8.670$, $p = 0.011$ ↓	$F_{(1,14)} = 6.338$, $p = 0.025$ ↓	$F_{(8,112)} = 4.435$, $p < 0.001$ ↑	$F_{(8,112)} = 4.523$, $p < 0.001$ ↓
HR	1 mg/kg	10 mg/kg	n.s. x	n.s. x	n.s. x	n.s. x	n.s. x
HR	1 mg/kg	15 mg/kg	n.s. x	n.s. x	n.s. x	n.s. x	n.s. x
HR	2 mg/kg	10 mg/kg	$F_{(1,16)} = 100.423$, $p < 0.001$ ↓	$F_{(1,16)} = 21.349$, $p < 0.001$ ↓	$F_{(8,128)} = 3.836$, $p < 0.001$ ↓	$F_{(8,128)} = 12.272$, $p < 0.001$ ↑	n.s. x
HR	2 mg/kg	15 mg/kg	$F_{(8,120)} = 6.531$, $p < 0.001$ ↓	$F_{(1,15)} = 7.888$, $p = 0.013$ ↓	$F_{(8,120)} = 4.119$, $p < 0.001$ ↓	$F_{(8,120)} = 4.081$, $p < 0.001$ ↑	n.s. x

and Anderson, 1981; Wagner and Anderson, 1982). The effects of 1 and 2 mg/kg of RES observed in the present study cannot be explained by impaired motor performance. First, the dose of 1 mg/kg of RES did not inhibit walking behavior during the first 40 min following 15 mg/kg of COC in LR (Fig. 5B). Second, the dose of 2 mg/kg of RES did not inhibit walking behavior during the first 30 min following this dose of COC in HR (Fig. 5B). Third, RES was found to increase, instead of decrease, COC-induced grooming (a behavioral item that highly depends on motor performance) in both types of rat that were treated with 15 mg/kg of COC (Fig. 7B).

4.6. Conclusions

Our findings nicely fit in with the previously reported findings by Hooks et al. that COC increases general activity less strongly in LR than in HR (see also Section 4.2). The present study, in which the effects of COC on distinct types of behavior were studied in more detail (see Methods), provides the original information that COC differentially affected each type of these behaviors in these rats (Section 4.2). The indole alkaloid RES strongly changed COC-induced behavior. A higher dose of RES was required to affect COC-induced walking, normal free rearing, normal wall rearing, grooming and repetitive wall rearing in HR than in LR (Sections 4.3 and 4.4). These results could not be explained by RES-induced changes in motor performance (Section 4.5).

There is ample evidence showing that COC-induced behavior is accompanied by an increase of monoamines in the brain (Amalric and Koob, 1993). We have previously shown that individual differences in the sensitivity to COC are most likely not due to individual differences in the re-uptake of these monoamines (Verheij et al., 2008). Accordingly, the observed RES-induced individual differences in behavior may very well be explained by our recently reported finding that LR are marked by a smaller monoaminergic storage pool than HR (Cools and Verheij, 2002; Verheij and Cools, 2009b; Verheij et al., 2008). We hypothesize that COC changed behavior less strongly in LR than in HR (Section 4.2), because COC can release less monoamines from storage vesicles in LR than in HR. Given that the observed individual differences in the behavioral effects of RES can only be explained when at least three different substrates are affected (Sections 4.3 and 4.4), we speculate that individual differences in monoaminergic storage capacity are not only limited to the dopaminergic system of the nucleus accumbens (see Introduction). In this respect it is important to note that LR and HR have been found to differ in the make-up and reactivity of their noradrenergic (Verheij and Cools, 2009b) and serotonergic (Verheij et al., 2009) systems as well (for review: Verheij and Cools, 2008).

4.7. Impact

The fact that RES strongly reduces the behavioral (presents study) and neurochemical (Verheij et al., 2008) response to COC opens the intriguing possibility that drugs that deplete monoaminergic storage vesicles may have therapeutic effects in the treatment of (the onset of) COC abuse (for review: Verheij and Cools, 2008). Two clinical trials on the effects of RES in COC-addicted subjects have already revealed promising results (Berger et al., 2005; Gorelick et al., 2004). However, Winhusen et al. (2007) were not able to confirm these results. In these studies only one single dose of RES was tested. The fact that no differences were found between RES and placebo treated COC users in the study of Winhusen et al. (2007) may well be explained by our finding that not all subjects are sensitive to the same dose of RES. It has to be noted that high doses of RES can have a number of side effects like hypotension and nasal congestion. It is, therefore, highly recommended to test for the clinical safety of newly developed drugs that act by depleting monoaminergic storage vesicles.

High and low responders to novelty rats are generally referred to as an animal model for high and low sensation seeking in man (Ballaz et al., 2007a, 2007b; Cools and Ellenbroek, 2002; Dellu et al., 1996). On the basis of our animal studies, it is hypothesized that COC-addicted individuals that are marked by high sensation seeking scores need higher doses of RES in order to elicit therapeutic effects compared to COC-addicted individual that are marked by low sensation seeking scores.

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